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Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer

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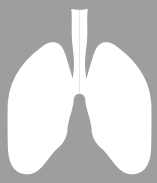
CHAPTER 4A

Detecting resistance in *EGFR*-mutated NSCLC after clonal selection through targeted therapy



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ABSTRACT

Tumour heterogeneity plays an important role in the development of treatment-resistance, especially in the current era of targeted therapies. Although tumour heterogeneity is a widely recognized phenomenon, it is at present unclear how this knowledge should be incorporated into daily clinical practice. In this report we describe an innovative nuclear imaging method that may play a role in detecting tumour heterogeneity in the future.

It is believed that cancer arises from a single common ancestor cancer cell (1). The development of this one cell to metastatic cancer is a multifactorial process, influenced by clonal selection, according to historical evolution theories. Genetic instability and epigenetic events lead to the survival of the 'fittest' clones and at time of clinical presentation, tumours consist of multiple molecularly distinct tumour cell populations (2). The populations with the highest proliferation rate predominate in the tumour lesions. Consequently a tissue biopsy or cytological sample for diagnostic purposes will most likely be procured from this dominating part. Subsequently, this small sample from the dominating part will be considered to be representative for the whole tumour, primary and metastatic lesions. Even till very recently the initially obtained tissue was the only sample used for decision-making throughout the whole treatment period, even far beyond first line treatment, despite the well-known and well-described phenomenon of tumour heterogeneity (3, 4). Physiological and iatrogenic events, for instance anti-tumour therapy, may modify the clonal selection process. With modern therapies that are aimed at a specific target, nowadays described as 'targeted therapy', this effect is even more pronounced than with traditional chemotherapy.

Treatment of epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) patients with tyrosine-kinase inhibitors (TKIs) results in high response rates and prolongation of progression free and overall survival. Unfortunately most patients develop progression after approximately 10 months, while on treatment. This pattern of progression is usually different from the behaviour prior to start of TKI-treatment. Several studies of rebiopsy at the time of tumour progression while on treatment, demonstrated that in more than half of the patients the new tissue sample differed from the initial sample (5). A common finding is presence of a different mutation at *EGFR* exon 20, the T790M mutation. This finding illustrates that in particular targeted therapies selectively eliminate sensitive clones, providing resistant populations of tumour cells the opportunity to outgrow. The outgrowth of certain tumour populations during a targeted treatment increases tumour heterogeneity, allowing both resistant and sensitive clones to be present simultaneously. This demonstrates the need for continuous mapping of sensitivities and resistances of the tumour in order to be able to tailor treatment to the individual patient; the basis of the principle of 'personalized medicine'.

The importance of tumour heterogeneity in the development of resistance to targeted therapies has extensively been described. Currently, the only way of detecting tumour heterogeneity is by sampling tumour tissue from different locations within the primary tumour and from different metastases, which is not feasible in daily clinical practice given the burden to the patient.

Here, we describe a patient who underwent two positron emission tomography (PET)-scans using radiolabelled TKI ([^{11}C]erlotinib) as tracer (TKI-PET), a promising tumour imaging method (6). It has been demonstrated that NSCLC tumours that harbour an activating *EGFR*-

mutation have higher TKI binding affinity compared to tumours with wild-type *EGFR* (7). Therefore, increased [^{11}C]erlotinib uptake is indicative of (parts of the) tumour lesions that are sensitive to TKI-treatment (8).

A 46-year-old Asian woman was diagnosed with *EGFR*+ (exon 19 deletion) NSCLC (T3N3M1b), in the right upper lobe (RUL). Prior to treatment with erlotinib, an [^{11}C]erlotinib PET scan was performed (8) (Figure 1A). The overall tumour [^{11}C]erlotinib uptake was quantified by pharmacokinetic analysis in a 2-tissue reversible model using volume of distribution (V_T) as a measure of uptake, as previously described (8). A tumour V_T of 1.33 ± 0.03 and 1.90 ± 0.04 was measured during test and retest, respectively. Homogeneously increased uptake of [^{11}C] erlotinib was observed both in the tumour and in enlarged mediastinal lymph nodes. After start of erlotinib in standard dosage the patient obtained a partial response that lasted for 18 months. Then, there was progression in the primary tumour and a biopsy of this lesion showed the known EGFR exon 19 deletion, and a T790M mutation (molecular analysis performed by EGFR/KRAS high resolution melting (HRM) pre-screen with sequential analysis confirmation (9)). The [^{11}C]erlotinib scan was repeated after discontinuation of erlotinib for approximately 1 week (Figure 1B). This scan showed a V_T value of 1.09 ± 0.02, indicating a decrease of 18% and 43%, as compared to test and retest, respectively. Also, by visual assessment, the intratumour [^{11}C]erlotinib uptake pattern had become heterogeneous, suggesting that also tumour affinity to TKI had become more heterogeneous. In retrospect the area where the new biopsy was taken, the dorsal part of the tumour, had little uptake of [^{11}C]erlotinib.

Applying this technique is not only a rather patient friendly method to illustrate the biological phenomenon of tumour heterogeneity and the limitations of the first generation targeted therapy drugs, but it may have consequences for guiding the clinician where to obtain a new biopsy in this specific situation. Although there is at this stage no registered targeted drug available for treatment after development of resistance through selection of the T790M clone, in the very near future promising drugs – e.g. CO1686, AZD9192- are expected, specifically targeted at T790M (10, 11). Switching to these next generation TKIs might again result in prolongation of progression free survival and survival. For today's situation, the [11C] erlotinib PET scan may indicate residual TKI sensitivity, helping clinicians to decide whether the TKI should be continued while standard second-line chemotherapy starts or should be restarted after finishing chemotherapy.

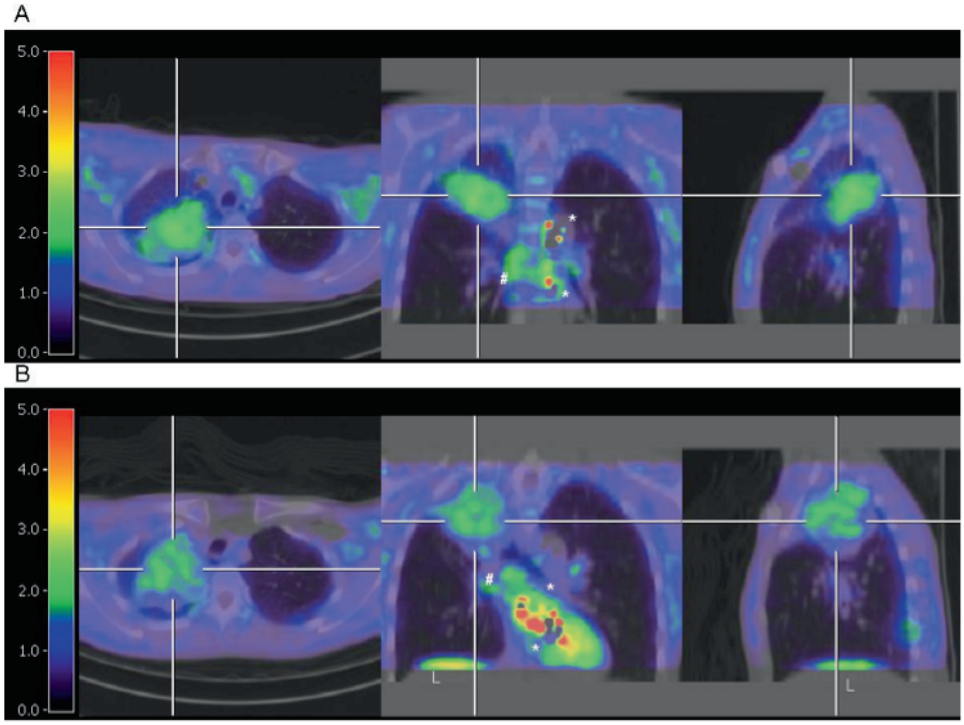

Figure 1: Positron emission tomography scan showing [^{11}C]erlotinib uptake in the tumour
(A) Prior to treatment
(B) After treatment with erlotinib